

KINETOSES

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16. Abstract <p>A presentation of materials on various aspects of the kinetoses. Studies of motion sickness, air sickness, automobile sickness, spacecraft sickness, etc. An investigation of certain mechanisms of the vestibular apparatus, nystagmus, the vegetative nervous system, and the somatic nerves. Neurophysiological explanations of possible mechanisms of motion sickness and ways of countering them. A review of the world literature on the subject.</p>			
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KINETOSES

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In recent years, thanks to enormous technical achievements and, in particular, to the use of new high-speed means of transportation, interest has greatly heightened in studying the pathological reactions related to the influence of changes in acceleration on the organism. This complex of symptoms, which appears during transportation in various transport facilities (on a ship, in an aircraft, in an automobile, etc.), can be characterized by the general term kinetoses or motion sickness. Particularly great significance has been acquired by the problem of kinetoses in connection with the development of space flights, in which man is subjected to the action of significant acceleration and weightlessness. /332*

The term "kinetoses" is customarily understood to mean the sensation of ill-being (in the case of inclination to their appearance) due to the action of long-term changing accelerations.

The Symptom Complex of the Kinetoses

The symptom complex of the kinetoses is made up of four types of reactions which are manifested differently in different people: 1) motor reactions, which are expressed in change in the tonus of the transversostriated musculature; 2) vegetative disorders, which are manifested in paleness, cold sweat, dyspeptic disorders, lack of appetite, aversion to food, nausea, and vomiting; one notes a decrease in the pulse rate and a weakness in blood vessel fullness; 3) sensory (or vestibular) reactions, which are characterized by dizziness and disorientation in spatial perception; 4) psychological ones — depressed state, asthenia, sleepiness, perceptual disorders, disorders of the attention, and clarity of consciousness; illusions are possible.

Graybel (1968) suggests distinguishing between two categories of symptoms. To one group he assigns symptoms which involve the systems which normally

*Numbers in the margin indicate pagination in the foreign text.

derive their innervation from the vestibular apparatus. These symptoms appear in a slowly rotating room; they include the following: sensation of spinning or rotation, visually apparent movement (Coriolis oculogyral illusions); Coriolis nystagmus, dizziness, and motor discoordination. These symptoms are characterized by a brief latent period, by a maximum of response to initial stimuli, by changeability under exposure to secondary influences, short duration, and variable adaptation time. To the second category the author assigns symptoms which involve systems not normally receiving their innervation from the vestibular apparatus, i.e., "ones absurd for the vestibular mechanism and human economy" (Figure 69). These can be caused by other means than motion. These /333 symptoms include all vegetative disorders and disorders of the metabolic processes. They are characterized by a long latent period, stability of the effects, direct dependence on the duration of exposure, and by a difference in adaptation. It is necessary to distinguish these symptoms from motion sicknesses or kinetoses.

The appearance of the kinetoses can be strengthened under the influence of stimulation of certain receptors (visual, cutaneous and motor), and are more pronounced in persons with heightened excitability of the sympathetic or parasympathetic region of the nervous system or the vestibular analyzer. Closing the eyes and eliminating bright light or sharply pungent substances frequently decreases dizziness and nausea. In some people, during long ship voyages or long trips in an automobile, the symptoms of the illness gradually diminish (in 95% of sensitive persons adaptation develops), while in others they can acquire a severe character (Tyler, Bard, 1949). However, up to the present time not a single case of lethal outcome has been described. After exposure to the changing accelerations has ceased, the symptoms of the kinetoses disappear. Only in the course of the first few hours afterward may the patients still sense nausea and lack of confidence during walking.

Etiology and Pathogenesis

One can consider the concept that spatial analysis is carried out by a /334 complex of analyzers in which a leading role belongs to the vestibular analyzer to be universally accepted. A. A. Ukhtomskiy wrote: "As a whole, the labyrinth is a powerful functional prerequisite for quantitative and computational

orientation of man in his environment, together with the apparatus of tactile and visual reception."¹

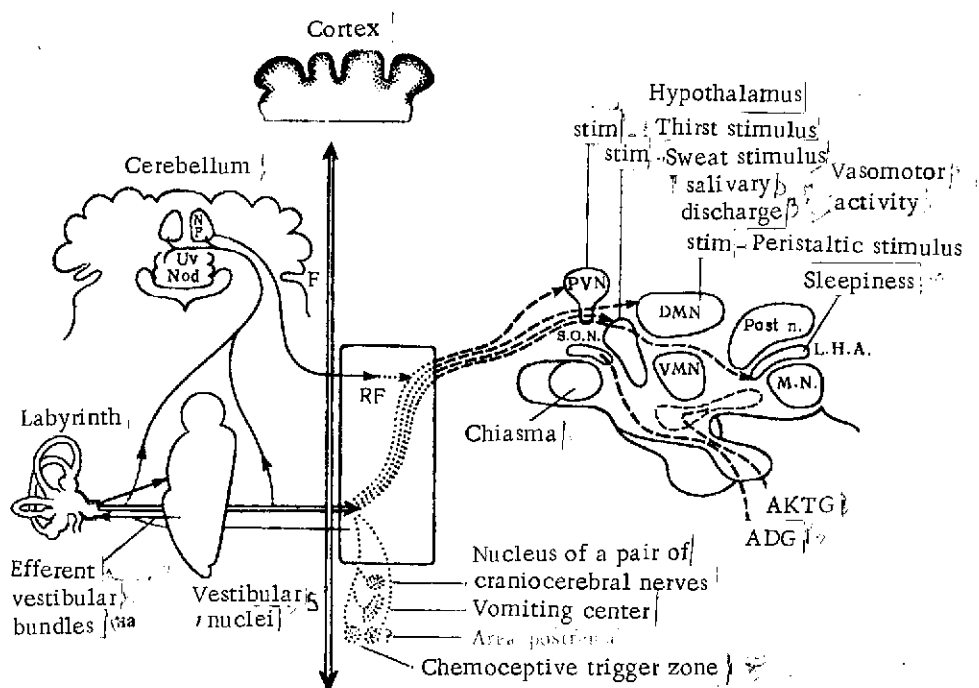


Figure 69. Diagram of Possible Irradiation of the Vestibular Activity (Dotted Line) Which Appears During Coriolis Acceleration (After Graybiel, 1968). NF, N. Fastigii; UV, Uvula; F, Floccule-nodular portion; RF, Reticular formation; Stim, Stimulation; PVN, Paraventricular ganglion; S.O.N., Supra-optic nucleus; DMN, Dorsomedial nucleus; VMN, Ventral medial nucleus; Post. n, Posterior nucleus of the hypothalamus; L.H.A., Lateral hypothalamic region; MN, Medial nucleus.

However, under the natural conditions of life the role of the vestibular analyzer consists not only in creating a comfortable posture for the body, but also in counteracting the effect of acceleration, the force of gravity, and rolling by mobilizing the most important vegetative functions. Therefore, the vestibular analyzer must be included among environmental analyzers (V. N. Chernigovskiy, 1967).

Inasmuch as the labyrinth is an organ which perceives acceleration, the labyrinth hypothesis of the pathogenesis of the kinetoses is the dominant one.

¹A. A. Ukhtomskiy. "Sobraniye sochineniy," [Collected Works], 1945, Vol. IV, p. 219.

It is supported by the following clinical observations. Among the deaf and dumb, for example, the symptom complex of the kinetoses is not observed (Graybiel, 1964, and others). Among children up to 2 years old, the excitability of certain analyzers, including the vestibular analyzer, is diminished, and therefore in these persons one also does not observe manifestations of the kinetoses. On the other hand, after the age of 40 sensitivity to change in acceleration increases (Tyler, Bard, 1949; G. M. Tsimmerman, 1967). However, in this hypothesis of the pathogenesis there is one vulnerable spot, inasmuch as in the clinical picture of kinetoses nystagmus is absent — nystagmus being the basic symptom of labyrinth damage.

Among horses, dogs, cattle, sheep and chickens, one observes a symptom complex of kinetoses, while rabbits, guinea pigs, pigeons, cats and apes prove resistant to change in acceleration. Dogs, in their turn, are equally as sensitive as man (Tyler, Bard, 1949). According to the labyrinth hypothesis, during roll there is supraliminal stimulation of the organ of equilibrium and hence of the other receptors.

It should be noted that the force of terrestrial gravitation limits the possibility of exposure to acceleration under natural conditions of life, particularly in organisms having a significant body mass. At the same time, if the intensity of action of other stimuli is limited by special mechanisms (for light — by the eyelids, for sound — by the muscle tightening the eardrum and the stirrup), then in the receptor which perceives the posture and movement of the body there will be no such mechanisms.

There are two viewpoints regarding the origin of the kinetoses: 1) hyperstimulation of the otolith system (V. I. Voyachek, 1909; G. deWit, 1953); 2) hyperstimulation of the cupular system (Graybiel, 1964, 1966). Lansberg (1963) critically analyzed the data of the authors indicated, specifically with respect to the magnitudes of linear and angular acceleration and advances a third viewpoint. In his opinion, the reason for the kinetoses is intralabyrinthine conflict caused by a difference in impulsation from the otolith organs and the semicircular canals. This in its turn complicates coordination of the activity of the brain centers. Such a situation appears, specifically, when the head is inclined backward and forward after rotation. In this case

the very same impulsation from the otolith organ is combined with an entirely different impulsation from the semicircular canals. Hence, the reason for the kinetoses consists in disruption of the standard level of movement stereotype which exists in the centers. /335

On the other hand, by means of studies of M. D. Yemel'yanov et al. (1962), it was shown that the thresholds of certain vestibulo-vegetative reflexes can be lowered under the influence of stimulation of other afferent systems (specifically, the visual analyzer or the proprioceptors) without significant change in the reactivity of the vestibular analyzer. Apparently, the function of the vestibular analyzer should not be considered outside of the context of its interrelationship with the other analyzing systems. Hence, according to this viewpoint, the kinetoses are the result of disorders in the interaction of the analyzers. This conception also includes intralabyrinthine conflict as a particular case. It could be that the absence of nystagmus could also be related to these very characteristics of interaction of the afferent systems, while the manifestation of unfavorable vegetative reactions could be related to a change in the functional condition of the effector center, which is the intermediary of the corresponding reactions.

Mechanics of the Semicircular Canals and Otoliths

We shall dwell only briefly on these problems. More detailed reports on the mechanics of the vestibular apparatus are given in the book by A. N. Razu-meyev and A. A. Shipov, *Nervnyye Mekhanizmy Vestibulyarnykh Reaktsiy* [Neural Mechanisms of Vestibular Reactions] (1969).

Steinhausen (1933) advanced the hypothesis that the cupola-endolymphatic system should be viewed as a high-friction torsion pendulum. In this case, the equation of movement of endolymph in the semicircular canals is determined by the balance of the forces of inertia, the elastic forces of the cupola, and the viscous friction, i.e.,

$$J\ddot{\theta} + C\dot{\theta} + K\theta = 0$$

$$\ddot{\theta} = -\frac{C}{J}\dot{\theta} - \frac{K}{J}\theta = 0,$$

where θ , $\dot{\theta}$, $\ddot{\theta}$ are, respectively, angular displacement, angular velocity, and angular acceleration of endolymph relative to the walls of the canal; J is the

moment of inertia of the endolymph ring; C is the coefficient of the moment of force of viscous friction; K is the coefficient of the moment of the force of elasticity (Groen, 1956).

An approximate solution of this equation for a case of high friction ($C \gg K$) shows that if the cupola is suddenly displaced at a velocity γ ("stop-stimulus"), then over a very brief period (on the order of 0.04 second) it is displaced at a maximum angle and will then slowly move to a position of equilibrium. Considering that the duration of nystagmus (T) which arises during the "stop-stimulus" is basically determined by the time of rotation of the cupola, one can obtain the expression:

$$T = \beta \ln \frac{\gamma}{\gamma_{thr}},$$

where γ is the velocity of uniform rotation before the stop ("stop-stimulus"), while γ_{thr} is the minimum (threshold) value of the "stop-stimulus", at which postrotational nystagmus appears; β is the coefficient of proportionality. The relationship of duration of postnystagmus to the magnitude of the "stop-stimulus", constructed on a semilogarithmic scale, is within certain limits a straight line whose tangent to the angle of inclination to the logarithmic axis is β .

By simultaneously recording the postrotational sensations one can obtain /336 similar curves. However, there is a difference between nystagmus and sensation. The inclination of the cupulogram of the nystagmus is steeper and its threshold is higher. A lesser inclination of the curves of sensation indicates the presence of central inhibition of the vestibular system (Groen, 1957). In persons daily subjected to exposure to accelerations of high magnitude, one observes gradual flattening of the curves of sensation and nystagmus, first of the curve of sensation and then the curve of nystagmus.

Hence, a healthy person has the capacity to influence the vestibular function in various branches of the vestibular tract. Such a fact is an example of inhibition characteristic of the central nervous system. One of the results of such inhibition is becoming accustomed to the roll of a ship. Most people at first become seasick, but finally become capable of tolerating ship roll.

Certain people never become accustomed even to slight roll (for example, Admirals G. Nelson and F. F. Ushakov). In such people the inclination of the sensation curves is greater than it is in healthy people.

The equation of movement of the otoliths is similar to the equation which describes the movement of endolymph in the semicircular canals. However, the time constant which characterizes the time of rotation of the pendulum from the inclined position to the position of equilibrium is 40 seconds for the cupola-endolymph system (Groen et al., 1952), while for the utricular otolith it is 0.05 seconds (DeVries, 1950). Naturally, the sensations which appear during stimulation of these peripheral organs are of the same magnitude (Egmond et al., 1952), and therefore investigations of the otolith sensations during exposure to short-term linear accelerations are practically impossible.

Under special conditions, when not only the force of terrestrial gravity but also linear accelerations are acting on a man, the effective force for the otolith formations will be the tangential component resulting from all forces and acting on the otolith. Therefore, for example, in the absence of visual orientation a man subjected to the effect of forces of acceleration will perceive a vertical which coincides in direction with such an effective force. A man whose field of view contains no orienting objects with respect to the Earth's surface will always place his body in space in accordance with the apparent direction of the vertical. If a contradiction arises in a man between the visual and the otolith information, this contradiction is always resolved in favor of the visual information.

Characteristics of Functioning of the Vestibular Apparatus During Sea Roll And Flights In Aircraft

In a state of calm the Earth's gravity acts upon the human organism, while during the passive movement of the human organism (aboard ship, in an automobile, etc.), to this force one adds linear or angular acceleration which are specific stimuli, respectively, for the receptors of the semicircular canals and of the otolith organs.

A mathematical analysis of ship movement has shown that during any roll it produces movement in the vertical plane and rotational oscillations. Consequently, during any roll the semicircular canals and the otolith apparatus are

subjected to stimulation. Roll includes movements of the ship during dead swells caused by elevation and immersion of the vast rolling mass. However, /337
not all types of roll cause seasickness.

Maximum acceleration during dead roll is 0.178 G ($G = 981 \text{ cm/sec}^2$) in a stormy sea and 0.214 G in very stormy seas. Minimum stimulus to the otolith apparatus is observed during vertical accelerations comprising 0.01 G. Consequently, during dead roll the degree of vertical acceleration significantly exceeds the sensitivity of the vestibular apparatus, which causes the appearance of the otolith symptom complex. During dead roll stimulation of the semicircular canals does not occur, since during dead roll angular accelerations are absent.

During side (lateral) roll, i.e., during movement of the ship about its longitudinal axis, the magnitude of stimulus of the otolith apparatus is five times higher than the threshold value. During keel roll, i.e., during movement of the ship about its transverse axis, acceleration of linear movement is ten times greater than it is during side roll.

It is important to emphasize that the mechanisms of appearance of seasickness have by no means been clarified. For example, the genesis of development of symptoms of the sickness during dead roll, during which linear acceleration is occasionally significantly less than it is during keel roll is not clear (Wit, 1953; G. S. Zimmerman, 1967).

The aircraft in three-dimensional space has 6 degrees of freedom of movement (3 in forward motion and 3 in rotating motion). As a result of this, constant changes in the magnitude and direction of the gravitational field and long-term rotating motion to which the pilot is usually subject are possible. Both the semicircular canals and the otolith organs can be stimulated. Vestibular information on orientation becomes an unreliable source. Therefore primary significance is given the visual analyzer. While under terrestrial conditions disorder in spatial orientation is nearly always linked with certain elements of pathology, disorders in spatial orientation in the air are quite frequently observed without any pathological disorders. This primarily occurs because the single reliable channel of sensory information available to the pilot in flight,

namely vision, is frequently limited to indirect objects of orientation, i.e., onboard aircraft apparatus.

Characteristics of Functioning of the Vestibular Apparatus in Weightlessness

In the space flight of G. S. Titov and in those of certain other cosmonauts, there were vegetative disorders. Inasmuch as these phenomena were reminiscent of the roll syndrome, naturally, the attention of investigators was directed toward a search for "Sputnik sickness" and toward explanation of the role of the vestibular apparatus in the development of unfavorable vegetative reactions. However, in solving this problem, significant difficulties arose.

Primarily, analysis of adequate stimuli of the vestibular apparatus in cosmonauts during complicated movements of the spacecraft has made it possible to establish the possibility of appearance of Coriolis accelerations. The magnitude of the latter, however, proved to be significantly below the threshold level. Theoretically, such stimuli of the receptor systems are beyond the limits of perception. In the second place, the experience of space travel indicates that vestibulo-spinal reflexes do not undergo significant changes in weightlessness. Consequently, gross disorders of vestibular function are not /338 observed. Apparently, notwithstanding the loss of weight by the otoliths, the inertial forces which appear during acceleration as the result of differences in the mass of the otoliths and the cellular filaments continue to operate. There is no basis to speak of inactivation of the receptor instruments of the labyrinth as Graybiel (1966) does. Finally, under conditions of weightlessness there are significant disorders in the central regulation of vascular reflexes and certain other reflexes, which of themselves can serve as a cause for the development of a syndrome similar to the roll syndrome.

Hence, one could mention the significant role of the vestibular analyzer and the development of the indicated syndrome in space flights under conditions of either a significant decrease in threshold sensitivity or possible accumulation in the centers of threshold stimuli with subsequent performance of the vegetative reflexes. All this has been complicated by the concept of mechanisms of "Sputnik sickness" — a syndrome going beyond the framework of ordinary concepts concerning seasickness (M. D. Yemel'yanov, A. N. Razumeyev, 1970).

Inasmuch as there are no directly recorded data with respect to the impulse activity of the vestibular receptors under conditions of orbital flights, the characteristics of functioning of the vestibular apparatus in weightlessness can be viewed as merely theoretical.

The mechanical structure and physical properties of the organs perceiving angular acceleration are such that one could hardly expect any changes in their functioning in weightlessness. Indirect affirmation of this concept is available in the work of Jackson (1966), who did not detect changes in the nystagmus reactions during rotation and caloric tests in weightlessness during flights of aircraft along a Kepler parabola.

The words of Bekesy (1953) on the snail, Flock's studies (1965) on the organ of the fish lateral line, and Trincker's studies (1962) on the utricle of the guinea pig showed that an adequate stimulus for the filament cells of otolith organs is a tangential component directed transversely to the filament — the so-called "shearing force". Trincker (1962) established that during strictly perpendicular extension or pressure on the otolith membrane one cannot cause a change in the constant potential in the layer of sensitive cells. Only forces directed at a tangent to the filaments caused depolarization or hyperpolarization and an increase or decrease in the electrical activity in the nerve. In weightlessness there is no force of weight but this should not lead to a change in the spontaneous impulsation in the utricular nerve if the membrane is uniform and occupies a strictly horizontal position in the skull relative to the longitudinal axis of the body. In reality the membrane has a complex shape and an inclined position; therefore during the absence of the force of weight the otolith should move somewhat under the influence of the elastic forces of the submembranous layer, which, judging by the experiments of Copee and Ledoux (1951), should lead to an increase in spontaneous impulsation in the utricular nerve. This is possibly explained by an increase in spontaneous impulsation in the neurons of the Scarpa ganglia, which has been observed in the cat in a weightlessness tower (Fiorica et al., 1962), and in the frog during flights of aircraft along a Kepler parabola (Gualtierotti, Gerathewohl, 1965). However, a slight quantitative change in impulsation in the utricular nerve could hardly produce such gross symptoms as nausea, vomiting, and vascular reactions.

During inclination of the head under terrestrial conditions, the terminal "instruments" of the semicircular canals and the receptors of the otolith organ are simultaneously stimulated. In weightlessness, what with the altered reaction of the otolith organ, intralabyrinthine conflict is possible: unaltered impulsation from the ampules of the semicircular canals can be combined with altered impulsation from the otolith organs. One can agree with the opinion of Lansberg (1963) to the effect that the intralabyrinthine conflict can form the basis of the development of pathological reactions. However, in all probability, it should be viewed as a "trigger" of some kind which leads to imbalance in the interaction of the afferent systems. /339

Physiological Mechanisms of the Kinetoses

The physiological mechanisms of the kinetoses are almost entirely uninvestigated. However, there are no doubts that the influence with respect to the vestibular apparatus dominates in the development of the syndrome of kinetoses. Therefore, the attention of investigators is directed primarily toward clarifying the role of the vestibular analyzer in the development of unfavorable disorders.

Thresholds of perception of angular acceleration for man are $6.09 \cdot 10^{-4}$ radian/sec² — $3.48 \cdot 10^{-3}$ radian/sec² (Clark, 1967). If one converts these values to the values of energy required to activate the sensing cells it turns out that the thresholds for cells in the cristas of the ampules of the semicircular canals the utricle and the saccule are equal (Groen, 1957). The thresholds of the response reactions to vestibular stimulation in the vegetative nervous system are three times lower (for n. vagus and n. splanchnicus) than they are in the somatic nerves (Germandt, 1964). From the studies of Trincker (1962) and of Shimazu and Precht (1965) it follows that sensitivity in various branches of the vestibular system, at any rate from the receptor to the vestibular nuclei, continuously increases. An increase in sensitivity at the level of the vestibular nuclei is linked with the presence in the latter of tonic and kinetic neurons (Shimazu, Precht, 1965). If the flux of vestibular impulses is not controlled at all, then with continuing increase in the sensitivity, with the very slightest movements of the head it would cause either vomiting or a complex of muscular activity. However, this does not occur. The flux of vestibular

impulses is progressively controlled by central commands and both the spatial and the temporal pictures are modeled at each stage of the system in accordance with influences coming in from the periphery. How does this occur?

The investigations of Sala (1965) and others have shown that the afferent influx of impulses to the vestibular system is altered under the influence of specific efferent nerve fibers (Petroff, 1955; Rassi, 1965, and others), according to the principle of inverse relationships. By analogy with the snail it is assumed that these efferent fibers exert inhibiting influences (Gernandt, 1967). Most vestibular impulses pass through the vestibular nuclei; however, Brodal and Hivik (1964) described primary vestibular nerve fibers leading to the cerebellum (nodulus, uvula, dorsal flocculus). Degeneration was traced in the musciform fibers near the Purkinje cells. Llinas et al., (1967) showed that stimulation of these fibers causes activation of the Purkinje cells. In their turn, the Purkinje cells exert inhibiting influences through the efferent fibers on the sensitive vestibular epithelium (Llinas, Precht, 1969) and on the neurons of Deiter's nucleus (Ito et al., 1966). Hence, the cerebellum exerts powerful inhibiting effects on the vestibular system at the level of the receptor-vestibular nuclei. On the same subject, there are data to the effect that the development of kinetoses is linked with the nodulus and uvula of the cerebellum (Bard et al., 1947).

Wilson et al., (1966, 1967) and also Ito et al., (1964) described a change /340 in the activity of neurons of the vestibular nuclei during stimulation of the nerves of the posterior and anterior extremities and of the afferent bundles in the spinal column. It turned out that spinal stimulation modifies the activity of the inhibiting neurons of the vestibular nuclei (Precht et al., 1967). Hence, in modifying the activity of the neurons of the spinal cord and the dorsal radicles (Erulkar et al., 1966), the vestibular system modifies its own activity on the inverse relationships model. To this one should add that Arslan and Molinari (1965) described tonic inhibiting effects of the cerebral cortex on the activity of the vestibular nuclei.

Interaction of the Vestibular Analyzer with the Vegetative Nervous System

The most exhausting symptoms of the kinetoses are the vegetative disorders. They determine the clinical picture of the kinetoses. Data in the literature

(Tyler, Bard, 1949; Shiraiwa et al., 1963, and others) enable one to hypothesize a certain instability of central control of the vegetative nervous system, which makes some people more sensitive than others. Apparently, hypo- and hyperreflex conditions are determined by the sum of the stimulating and the inhibiting influences on the vegetative and somatic nervous systems.

Vegetative disorders linked with the kinetoses, in the opinion of Ya. A. Egolinskiy (1967), should be divided into early and late disorders. The early disorders, which appear during vestibular stimulation, are classified by the author as changes in respiration, circulation, functions of the sweat glands, activity of the digestive organs, and body temperature; to the late changes he assigns changes in metabolism, the endocrine organs and the blood system. This group of disorders is preserved even after the end of vestibular stimulation. The characteristics of vegetative disorders are also cited in surveys of Spiegel (1946), S. N. Khechinashvili (1958), and others. Doubtlessly, such symptoms as sleepiness, paleness of the face, cold sweat, increase in salivation, and nausea and vomiting are related to the coordinating activity of the vegetative and somatic nervous systems. Apparently, afferent vestibular impulses reach centers of the vegetative nervous system but virtually no study has been devoted to their paths. Graybiel (1968) considers that decompensation, being expressed in the form of vegetative disorders, is determined by generalized vestibular impulsation in the reticular formation and hypothalamus. However, the author has no concrete proof and apparently there are more complex mechanisms which are linked, in our opinion, with the removal of inhibiting influences of the cerebellus on the vestibular system. A study of the tonic and kinetic control of the vegetative nervous system, and also of the paths and physiological characteristics of central processes related to the passage of impulses from the vestibular apparatus to centers of the vegetative nervous system and along its efferent fibers, will make it possible to reveal the mechanisms of the kinetoses. Work in this regard has only begun.

An interesting investigation of the functional condition of the respiratory neurons (located in the lateral zone of the medula oblongata) with adequate stimulation of the labyrinth (roll) was conducted by L. A. Radkevich (1969). She found that the respiratory neurons are extremely sensitive to such stimulation. Reaction to roll in some neurons occurred in the first second of

exposure and in others by 10th to the 15th second. Three types of reactions were established: 1) increase in spike activity of the neurons, on the average by 35-40% in comparison with the background frequency (75% of the neurons); 2) dropping off of impulse activity of the neurons, on the average by 25-40%; 3) absence of visible reaction (about 3.5% of the neurons). The volleys of discharges of the expiratory neurons lengthened while those of the inspiratory neurons shortened. If a discharge volley was more prolonged than the period of roll, then roll waves appeared in the correlation function (Figure 70). Breathing diminished, "harmonizing" with the rhythm of roll. It should be noted that this phenomenon of rhythm tied to impulse activity of neurons is not always manifested in external breathing. In those same cases when the respiratory movements were adapted to the rhythm of roll, this adaptation was manifested earlier in the impulse activity of the neurons and only after 3-5 seconds was it noted in the external respiration. It is extremely interesting that neurons with an incorrect rhythmic activity during roll could begin to generate volley discharge activity, and on the other hand, the neurons which had correct volley discharge activity in the original picture began to generate incorrect rhythmic activity. Among certain animals with the labyrinth apparatus removed, there was a sharp decrease in volley discharges and during roll no changes were observed in the correlation functions.



Figure 70. Autocorrelation Functions of the Interspike Intervals of the Respiratory Neurons Before Roll and During Roll. The appearance of waves corresponding to the rhythm of roll in the correlation function (L. A. Radkevich, 1969). a, Background activity; b, Activity during roll.

In a series of experiments a study was made of the reaction of neurons of the respiratory center to roll on alteration of functional condition of the respiratory center (bilateral vagotomy, administration of 1 ml of a 1% solution of lobeline and ethaperazine in a dose of 0.2 mg/kg weight of animal). Following vagotomy significant changes in the spontaneous activity of the neurons were not observed. Roll in the

vertical plane under these conditions caused a dropping off of respiration with disruption of the structure of the respiratory cycle (phase of inspiration

shortened, phase of expiration lengthened). The respiratory neurons of the vagotomized animals reacted to the stimulus in greater degree than was the case among intact animals. There was a twofold increase in the number of neurons with incorrect rhythm, an increase in the percentage of neurons which reacted with a change in the duration of discharge volleys. However, the phenomenon of association of rhythm with external respiration did not appear.

Against a background of administering lobeline, adequate stimulation of the labyrinth caused minimum reactions of the respiratory neurons in comparison with the reactions in animals with unaltered functional condition of the respiratory center. A large portion of the neurons investigated belonged to the third type (80%), i.e., they did not have visible reactions to altered average frequency of impulsation during roll. Change in the frequency of impulsation in the recorded neurons with respect to increase or decrease was slight. The volley-discharge respiratory neurons maintained the character of their activity in accordance with the phases of the respiratory cycle. Blockage of the reticular formation by means of ethaperazine caused a slight decrease in the reaction of the respiratory neurons to roll. The basic mass of neurons did not alter their average frequency of impulsation (about 70%), and in the remainder the frequency of impulsation either increases or decreased. However, these reactions were short-term ones and in most cases the activity was reestablished 20 seconds after exposure. "Fine sensitivity" to roll, which was expressed in the appearance of the periodic change in interspike intervals, was maintained. This fact permits one to hypothesize direct links between the respiratory neurons and the vestibular system (receptor, neurons of the vestibular nuclei). /342

S. N. Malikova (1969) studied the character of the rhythmic activity of the cardiovascular neurons during roll. Three series of experiments were conducted. Some animals (cats) were kept under light chloraloso-nembutal anesthesia (40 mg/kg chloralose + 10 mg/kg nembutal), while others were immobilized with a 2% solution of diplacine (1.5 mg/kg weight per hour), and still others were subjected to labyrinth destruction. Among the animals the impulse activity of the neuron in calm, during altered arterial pressure, in the period of reestablishment of arterial pressure, during stimulation of the vestibular

apparatus (roll), and during the after-effect period was recorded. The experiments were conducted only on neurons which altered their impulse activity to reflect change of arterial pressure. All of the recorded neurons (283) were spontaneously active. Five types of reactions of neurons to roll were discovered. Most neurons reacted with uniform continuous impulses (depressor and pressor), while during inflation of the urinary bladder there was a decrease in the frequency of impulsation (in the first series among the animals with the chloraloso-nembutal solution — 30.7%, in the second — in those immobilized with diplacine — 32%). Other neurons increased the frequency of impulse activity (in the first series 20.8%, in the second 16%). In the third group of neurons a "bunching" character of spontaneous activity was revealed. In certain of these such activity was revealed at the 10th to 12th second and was maintained during the period of after-effects, while in others background activity was reestablished (in the first series 12.2%, in the second 10%). In the fourth group of rhythmic neurons phase changes in activity were found which were expressed in an initial increase (at the 1st to 3rd second) and subsequent increase in impulsation (at the 6th to 12th second), or vice versa. In the fifth group of neurons no visible reaction to roll was found (in the first series 18.4%, in the second 30%). In the third series of experiments (bilateral destruction of the labyrinth apparatus), changes in impulse activity of the vasomotor neurons during roll were not observed, which indicates the vestibular nature of the described phenomena.

R. A. Grigor'yan and S. N. Malikova (1970) investigated reactions of the vasomotor neurons to direct electrical stimulation of the vestibular nerve. 53 vasomotor neurons were subjected to study. On the basis of the material obtained, all of the neurons investigated can be divided into two groups. Short lateral neurons, characterized by rapid responsive reaction with a short latent period (0.3-0.5 ms), comprise 25% of the total number of neurons investigated. Neurons with a long latent period of activation equal to 7-9 ms comprise 75% of the neurons (Figure 71). These data can apparently be explained by the fact that a slight portion of the neurons of the vasomotor center can be innervated monosynaptically by primary vestibular afferents, since a significantly greater number of neurons are activated through an intermediate relay

which obviously includes the triangular nucleus and certain cellular groups of the vestibular nuclei.

Akert and Gernandt (1962) and Gernandt (1964) studied the effect of electrical stimulation of the vestibular nerve on the potentials of n. vagus, n. phrenicus, and the sympathetic nerve bundles removed from a. carotis. The latency period of the responses was 4-5 ms. Stimulation of the vestibular nerve increased the respiratory discharges recorded in n. vagus. If the response was recorded between two spindles, the amplitude of the response was large and one could observe a delayed response. If in fact the response to stimulation of the vestibular nerve was added to the spindle activity of the respiratory center, the response was sharply inhibited and no second response was visible. With prolonged stimulation of the vestibular nerve the effect of temporal summation of responses in n. vagus was not detected, but was clearly revealed during the recording of potentials in n. phrenicus. The thresholds of the response reactions in n. vagus were 3 times lower than in n. phrenicus (Gernandt, 1964). /343

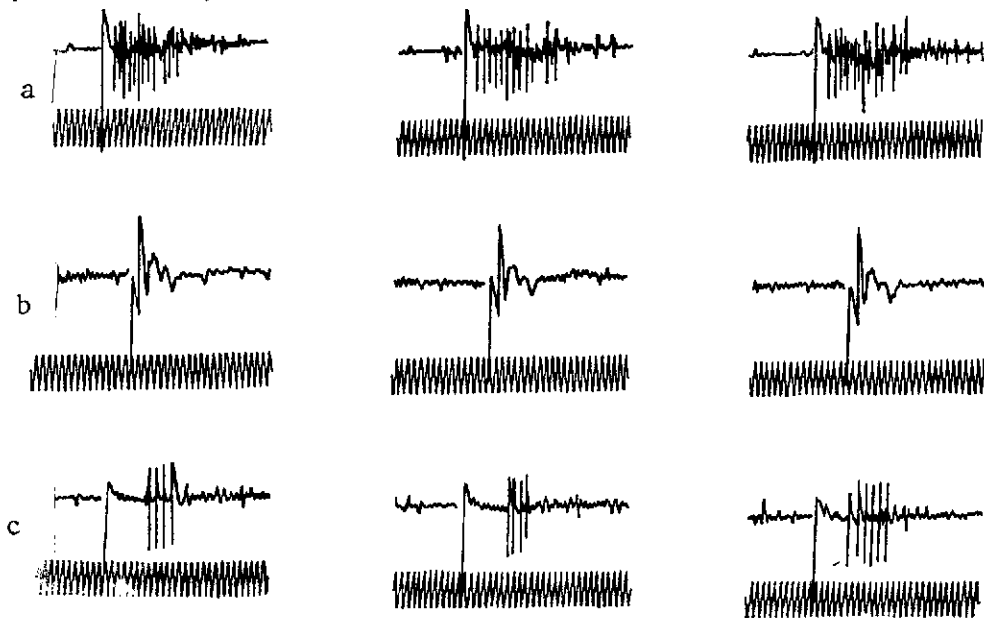


Figure 71. Discharges of Various Vasomotor Neurons in Response to Single Electrical Stimulations of the Vestibular Nerve (R. A. Grigor'yan, S. N. Malikova, 1970). a, "Bunching" response to single stimulation (5 V); b, Single impulses of second cell in response to threshold stimulation (5 V, latent period 0.3 ms); c, Response of third cell to electrical stimulation (5 V, latent period 8 ms).]

Megirian and Manning (1967) demonstrated that stimulation of the vestibular nerve entirely eliminated response reactions in n. vagus and n. splanchnicus to subsequent stimulation of nerves of the posterior extremity over a period of 190 ms. If the order of stimulation was reversed, i.e., there was initial stimulation of the nerves of the anterior extremities, then responses to subsequent stimulation of the vestibular nerve slightly decreased in proportion in n. vagus and completely disappeared in n. splanchnicus. In these experiments, responses to vestibular stimulation were earlier recorded in the orbital cortex and then in the peripheral vegetative and somatic nerves.

Cobbold et al., (1968) noted that in cats under curare anesthesia, during /344 stimulation of the vestibular nerve in n. splanchnicus, early (8-10 ms) and late (60-65 ms) responses are recorded; in the cardiac sympathetic nerve responses are recorded only with a prolonged latent period (75-90 ms), as is also the case in the abdominal sympathetic circuit (100-110 ms). Such responses with a prolonged latent period indicate that impulses from the labyrinth are widely propagated throughout the sympathetic circuit. In the opinion of the authors, these responses are linked with the cortico-diencephalic level. In its turn, the sympathetic nervous system influences the function of the terminal vestibular organ. Thus, Hojo (1963) demonstrated that after removal of the upper cervical ganglia in the rabbit, spontaneous and positional nystagmus appeared. Postrotational nystagmus immediately after the operation decreased and the reactions of the labyrinth to external and internal stimuli were stronger. The histological picture immediately after the operation revealed expanded blood vessels and edema of the labyrinth, while in later periods the edema disappeared but the vascular changes remained.

Spoendlin and Lichtensteiger (1966) established that adrenergic innervation of the sensitive epithelium of the labyrinth was accomplished by vegetative nerve fibers following blood vessels and by fibers running directly to the sensitive epithelium. The adrenergic nerve fibers were found in the cristae of the ampules and utricle and were absent from the walls of the utricle in the semicircular canals. It is extremely probable that stimulation of these efferent nerves can alter the sensitivity of the circular vestibular organ. It has been shown, for example, that pressure on the central artery of the retina raises thresholds of stimulation of the static organ.

In 1937 Hill advanced the conception that the kinetoses occur against a background of hyperactivity|of the parasympathetic system. Most investigators support this viewpoint. It is supported by clinical observations which indicate decrease in pulse frequency, decrease of arterial pressure, etc. However, Tang and Gernandt published a study in 1969 in which they cite data that the kinetoses, to the contrary, occur during hyperactivity of the sympathetic system. In experiments on curare-anesthetized cats, the authors showed that fluctuation of respiratory discharges in n. vagus were found only in the cervical region and were absent from the thoracic and abdominal regions. This is linked with impulsation in the recurrent laryngeal nerve which, as is known, derives from the dorsal motor nucleus of n. vagus and thus is a somatic nerve. Tang and Gernandt (1969) established that threshold stimulation of the vestibular nerve causes an increase in arterial pressure. On the other hand, when its ascent reached a peak, impulsation in the sympathetic nervous circuit decreased. The authors linked this fact with influence on the vestibular system of impulsation from the interoreceptors of the blood vessels.

On the basis of the data obtained they considered that the significance of the sympathetic nervous system in the pathogenesis of the kinetoses has been underestimated and they suggest that such symptoms as atony, suppression of peristaltis, paleness, cold sweat, increase in arterial pressure, hypersalivation, etc. are related to activation of the sympathetic nervous system under vestibular stimulation. However, these data as well should not be considered decisive. Apparently, matters are somewhat more complex. Before impulses from the labyrinth reach the complex of vegetative center nuclei, they pass through the vestibular nuclei and the reticular formation. Any tonic or physical influence on this intermediate relay alters the character of the vestibular influences on the vegetative and the somatic system.

We have already dwelt on Graybiel's concept (1968) concerning the role of /345 the hypothalamus in the pathogenesis of the kinetoses. Ban (1964) showed specifically that the medial preoptic zone and the media hypothalamus (sympathetic region) are closely interrelated to the vestibular nuclei via the dorsal bundle of efferent and afferent nerve fibers which possibly pass through the interstitial Kakhal nucleus and the central gray matter. It is through these links, in the author's opinion, that the sympathetic effects during stimulation

of the labyrinth are accomplished. We consider that the balance of the sympathetic and parasympathetic system in the pathogenesis of the kinetoses is determined by the cerebellum and the removal of its inhibiting effects on the hypothalamus and the nucleus of n. vagus. However, this problem still requires a detailed study.

The absence of temporal summation which was observed by Gernandt (1964), can be explained by the cytological characteristics of the cells of the dorsal motor nucleus of n. vagus. The cells of this nucleus are small with scattered but long dendrites. One could expect that the neuropil forming the telodendria is activated during vestibular stimulation and that the tree-like branching of n. vagus could not maintain adequate linkage for passing the vestibular impulses. The effect of temporal summation on the effector organ of the vegetative nervous system can apparently be explained by the liberation of acetylcholine and substances similar to it and also by the liberation of catecholamines.

Differences in thresholds for the vestibular and somatic systems can explain why, during the kinetoses, symptoms affecting the internal organs predominate at first. Impulsation from the respiratory center prevents influx of vestibular impulses to the nucleus of n. vagus. This control is inadequate to prevent the development of the syndrome of kinetoses. At the same time, the favorable effect of deep breathing on nausea is well known. Impulsation from the vestibular nuclei causes effects which lead to activation of many receptors (the proprioceptors of the muscles, blood vessels, tendons, the Pacinian corpuscles of the intestines, etc.). From them a flux of impulses can have an effect on modulating the activity of the parasympathetic and sympathetic systems. Whether this is achieved through the higher vegetative centers or the reticular formation is a question which remains open.

Prophylaxis and Treatment

A search for means for treating the kinetoses has been complicated by an almost total absence of reports concerning mediators in the relay branches of the vestibular system. Apparently, there are several relays. Jamamoto (1967), established that administering ionophoretic acetylcholine and noradrenaline stimulates the neurons of Deiters' nucleus. For noradrenaline this is unusual, inasmuch as it inhibits neurons of the olfactory tract, the cerebral cortex,

the hypothalamus, and the caudate body. However, the administration of atropine and dicholinisoproterenol did not block relay of afferent impulsation during electrical stimulation of the vestibular nerve. Probably both these mediators can be relays in the paths from the reticular formation and the cerebellum.

Obata et al., (1967) demonstrated the significance of γ -aminobutyric acid as a mediator in Deiters' nucleus. Ten Bruggemeate and Engberg (1969) confirmed these data and additionally demonstrated the role of clycine, which has been evaluated recently by many authors as an inhibition mediator.

Ye. L. Epshteyn and A. A. Shipov (1970), in experiments performed on guinea /346 pigs, studied the influence on the following nystagmus, after unilateral labyrinthectomy, of the M-cholinolytics (1 mg/kg methamycil), and the N-cholinolytics (5 mg/kg pediphen), an inhibitor of cholinesterase (1 mg/kg armine), an experimental adrenolytic (10 mg/kg), an adrenomimetic (10 mg/kg ephedrine), and amylthiourea (100 mg/kg). After administering the methamycil, pediphen and / amylthiourea the frequency of nystagmus at first sharply decreased and then slowly decreased. Ephedrine also decreased the frequency of nystagmus, while armine and the experimental adrenolytic, on the other hand, sharply increased it. These observations provide the basis for assuming participation of the acetylcholine-acetylcholinesterase system in mechanisms of relaying vestibular impulsation at the level of the central structures. Inasmuch as blockage of the choline reactive systems of the brain suppresses nystagmus while blockage of the adrenoreactive systems activates nystagmus, one can assume that the cholinereactive|neurons participating in passing on the vestibular afferent impulsation are stimulative ones, while the adrenoreactive are inhibitory. The method used does not exclude the influence of neurotropic preparations on the receptor structures which are both cholinereactive and adrenoreactive. Amylthiourea decreased the frequency of nystagmus just as effectively as the preparations having a cholinolytic effect. One of the possible mechanisms of suppressing nystagmus in this case is an increase in inhibition with respect to the cerebral cortex (stimulated under the influence of products of amylthiourea oxidation) on the vestibular nuclei.

The means employed for treatment and prophylaxis of the kinetoses are associated on the basis of their depressing effect on the vomiting center. A

survey of structural formulas shows that it will be hard to find a single structural-functional relationship until our knowledge of mechanisms of the pathogenesis of the kinetoses has been expanded.

Means employed for the treatment and prophylaxis of kinetoses can be divided into four groups: 1) anticholinergic; 2) antihistamines; 3) tranquilizers; 4) composite means. We do not consider it vital to cite all the employed preparations and will dwell only on the most effective and promising ones.

The preparation selected is a representative of the first group — scopolamine (0.6-1 mg — 90% effective). Of the antihistamine preparations, a great deal of attention has been drawn to derivatives of piperazine, specifically marezine or cyclizine (hydrochloride-1-methyl-4- α -phenylbenzylpiperazine). In a dose of 50 mg it yields 85% effectiveness during seasickness and 100% effectiveness during air sickness (Kimball, 1955; Lederer, Kidera, 1954). The preparation has almost no side effects but is characterized by short-term action. The effectiveness of the preparation plus the absence of side effects permitted its inclusion in the onboard pharmacy of the Apollo program (Berry, 1969) for prophylaxis and treatment of vestibulo-vegetative disorders. Of the tranquilizers, one should note thiethylperazine (thorecane). In a dose of 10 mg preparation, in 78% of the cases, it has an effect on seasickness. Its effect is due to accumulation in the cerebellum and the vestibular nuclei (Rubin, 1964). Two preparations attract attention in the composite group: tigan and diphenidol. Tigan is trimethobenzamide. It is used orally in a dose of 250 mg. In this dose the preparation does not have side effects. Apparently, its anti-vomiting influence is caused by its effect on the trigger zone of the vomiting center. However, it was not effective for treating motion sickness. A powerful anti-vomiting action and the absence of side effects has made it possible to recommend and include this preparation as well as marezine in the spacecraft pharmacy used by American astronauts (Wood et al., 1965). Diphenidol- α (α -diphenyl-1-piperidine-butanol-oxychloride) is used in a dose of 50 mg internally. In this dose the preparation does not have a side effect and has a powerful anti-vomiting effect. The spectrum of its therapeutic effect is extremely broad. It is suggested that diphenidol- α has an effect on the trigger zone and the "true" vomiting center (Leonard et al., 1966). Its influence on

/374

the vestibular system is not excluded either. In any case, diphenidol is among the selected antivomiting preparations.

The treatment and prophylaxis of kinetoses should be brought about by means of a complex of remedies. Searches for various combinations in the USSR are being carried out intensively (P. I. Syabro, 1965; M. I. Nikol'skaya, 1966, and others). However, a great deal of work yet remains to be done in this regard.

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